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Late Loss in Lumen Diameter and Binary Restenosis for Drug-Eluting Stent Comparison

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Background—Published rates of coronary restenosis have fallen below 10% in drug-eluting stent trials. Early evaluations of new stents have used continuous end points that are presumed surrogates for restenosis, but the generalizability and power of such end points have not been examined systematically.

Methods and Results—We examined the relationship between incremental changes in observed late loss in lumen diameter and the probability of restenosis using reported late loss from 22 published trials of various types of stents (bare-metal, drug-eluting, and small-vessel stents). Next, the power of late loss differences was compared with that of corresponding binary restenosis rates. The relationship between mean late loss and its SD was linear and did not vary with stent type (drug-eluting or bare-metal) or vessel diameter. At all levels of late loss examined (0 to 1 mm), incremental changes were associated with increasing restenosis risk (with an increasing magnitude of effect at higher levels of late loss). The power to detect a treatment effect was greater for late loss than for binary angiographic restenosis (≥32% relative increase in power, ≥24% absolute increase for late loss between 0.2 and 0.6 mm).

Conclusions—Late loss is monotonically related to restenosis risk in published stent trials. It is a generalizable and powerful angiographic end point in early or small trials of new drug-eluting stents. (*Circulation*. **2005;111:3435-3442.**)

Key Words: angioplasty ■ coronary disease ■ restenosis ■ stents ■ trials

Coronary restenosis after successful stent implantation is measured by a variety of methods that seek to quantify either the magnitude of renarrowing or the incidence of late-term clinical failure.[1] The assessment of coronary restenosis as a renarrowing process is performed ≈6 to 9 months after stenting with the use of quantitative angiographic and intravascular ultrasound metrics such as percent diameter stenosis or percent volume obstruction.[1–4] The assessment of coronary restenosis as a failure event utilizes dichotomous end points, such as the occurrence of a 50% diameter stenosis or clinically driven repeated target lesion intervention at follow-up, that signify a critical amount of renarrowing associated with resting flow or flow reserve obstruction.

Successful drug-eluting stents have reduced angiographic restenosis rates by ≥75% compared with bare-metal stents, resulting in binary angiographic and clinical restenosis rates of only 5% to 10%.[5,6] Because low binary event rates result in decreased statistical power in randomized trials, the number of patients needed to make comparisons between new and proven drug-eluting stents has increased substantially. Continuous end points such as follow-up minimum lumen diameter (MLD), percent diameter stenosis, and late loss have been used to test new stent technologies, particularly in early-phase, small–sample size trials, because of their inherent greater statistical power.[7–9]

Whereas relative measures of restenosis, such as percent diameter stenosis, depend on vessel diameter for their calculation and interpretation, absolute measures of restenosis magnitude can be more easily compared across trials of varying vessel size. Late loss, defined as the difference between immediate postprocedure MLD and MLD 6 to 9 months after percutaneous coronary intervention,[10] is an angiographic measure of the absolute amount of renarrowing. Specifically, it measures the change in MLD of the treated coronary segment due to vascular contraction and neointimal hyperplasia.[11] A general model adjusted for acute gain was developed in 1993 that directly related late loss to the incidence of binary restenosis.[1,12] For coronary stents, which by design resist vascular contraction and generally achieve a uniform lumen diameter within the stented segment, late loss is an angiographic surrogate for neointimal hyperplasia, the target of drug-eluting stents.[11]

Within the sirolimus-eluting stent trials, mean late loss is correlated with the probability of angiographic and clinical restenosis.[13] We sought to determine (1) whether this correlation between mean late loss and restenosis rates was generalizable to other stent studies and (2) whether the use of late loss as an end point in modest-sized clinical trials would be more powerful than the traditional binary restenosis end points. Specifically, we hypothesized that late loss in drug-eluting stent trials is a monotonic measure of restenosis risk, and we developed a model of late loss for evaluating contemporary drug-eluting stents.

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Methods

Literature Selection and Data Evaluation

A comprehensive MEDLINE literature search produced original reports of 22 clinical trials testing drug-eluting or bare-metal stents for the treatment of de novo coronary lesions that included late loss as an end point.[5,6,8,14–33] To evaluate the effect of variation in reference vessel diameter across trials, trials of small-vessel stenting were also included. Reports of stenting for total occlusion, ostial or left main lesions, saphenous vein grafts, and in-stent restenosis were excluded.

Definitions

Late loss was defined as the difference between the MLD immediately after the procedure and the MLD at 6- to 8-month follow-up. *Percent diameter stenosis* was defined as [1−(MLD/reference vessel diameter)]×100. *Binary angiographic restenosis* was defined as a >50% diameter stenosis at follow-up. To evaluate the relationship of mean late loss to both binary angiographic restenosis and its standard deviation (SD), the in-stent rather than in-segment (including the 5-mm margins proximal and distal to the stent) late loss was used because in-segment measurement was not available in most studies (Tables 1 and 2).

Statistical Analysis

Baseline clinical and angiographic variables were recorded as mean and SD for continuous variables and percentage for binary variables.

Evaluation of Monotonicity of Relationship Between Mean and SD of Late Loss

We performed regression analysis on the SD of in-stent late loss for each trial with mean late loss as the predictor variable. We tested linear, nonlinear (using polynomial terms), and interaction effects (for drug-eluting versus bare-metal and for small-vessel versus non–small-vessel stenting). A 2-sided P value ≤0.05 was considered significant.

Power Transformation for Late Loss Distribution

In drug-eluting stent trials, distributions with low late loss (in which the mean late loss value is a fraction of the SD) require transformation to account for right-skewed data, whereas higher late loss distributions (as in bare-metal stents with mean late loss values ≈1 mm and relatively smaller SDs) do not require transformation for normality.[13] We estimated the power transformation necessary to overcome the magnitude of rightward skew by interpolating the optimum power between those of the drug-eluting and control arms of the SIRIUS trial, anchored at mean late losses of 0.17 and 1.0 mm, respectively.[13]

Predication of Binary Restenosis Rate From Mean In-Stent Late Loss

The power transformation model was used to predict the binary angiographic restenosis rate from late loss. Essentially, the transformed mean and SD were used to estimate the probability of exceeding the transformed late loss threshold for binary restenosis by integrating the area under the cumulative distribution function. The predicted probability of restenosis, assuming a given mean MLD and reference diameter, was calculated for varying mean late loss from 0 to 1.0 mm, in 0.1-mm increments.

Power Comparison (Late Loss Versus Binary Angiographic Restenosis)

The powers of the end points late loss and binary angiographic restenosis were compared with the example of a hypothetical trial designed to detect a 35% treatment effect between 2 stents using 200 subjects per arm. In the range of late loss values from 0 to 1.0 mm, power was estimated for a 35% treatment effect on the end point of late loss and compared with the power of the corresponding predicted restenosis rates and treatment effect from the model.

Results

Study Characteristics

Summary statistics for late loss and binary angiographic restenosis rates are listed in Tables 1 and 2 for 22 stent trials.[5,6,8,14–33] In-stent late loss was widely reported for all studies of bare-metal stents and ranged from 0.65 to 1.21 mm, whereas in-stent late loss for drug-eluting stents ranged from −0.01 to 0.81 mm. In-segment late loss was rarely reported in the bare-metal stent studies. The range of residual stenosis after stenting was wide (1.7% to 19.8%), with a trend toward low residual stenosis in the recent pivotal drug-eluting stent trials TAXUS IV and SIRIUS (4.2% to 6%)[5,6] compared with the early stent studies STRESS and BENESTENT (19% to 22%).[16,27] The prevalence of diabetes mellitus varied from 0% to 31%. Mean reference vessel diameter ranged from 2.50 to 3.07 mm for the standard stent studies and from 2.23 to 2.55 mm for the small-vessel studies.

Late Loss Is Positively Correlated With Restenosis Rate

A generalizable correlation across bare-metal stent and drug-eluting stent trials would be required for late loss to serve as a valid surrogate for binary restenosis. Two analyses were performed to establish the nature of this relationship: (1) an analysis of the relationship between observed mean late loss from each trial and the corresponding observed restenosis rates and (2) an analysis of the relationship between the mean late loss and the corresponding SDs.

Late Loss Is Related Monotonically to Binary Restenosis

The relationship between mean in-stent late loss and restenosis rate for all study samples was found to be curvilinear and monotonic (Figure 1), that is, higher mean late losses were associated with higher reported rates of binary angiographic restenosis. Interaction terms for bare-metal versus drug-eluting and small-vessel versus non–small-vessel stenting were nonsignificant, with no apparent heterogeneity of the relationship across these categories.

SD of Late Loss Is Related Monotonically to Its Mean

If the relationship of the mean and SD of late loss does not follow a monotonic relationship, identification of a population with a higher mean but lower SD than an existing reference could occur, creating the theoretical possibility that a higher mean would be associated with a lower restenosis rate. Such a paradoxical situation would make interpretation of mean late loss values complex. In contrast, we found that the relationship between the late loss mean and SD was monotonic across the 22 trials with reported in-stent late loss (Figure 2), suggesting that conditions for such a paradoxical relationship did not exist. Linear regression revealed that the relationship between mean and SD was best described with the following function: SD of late loss=0.33+0.31×mean late loss in millimeters.

Comparative Efficiency of Late Loss and Binary Angiographic Restenosis

Power calculations for the restenosis end points late loss and binary angiographic restenosis were compared for a hypothetical stent study of modest sample size (200 subjects per arm). As

TABLE 1. Baseline and Procedure Characteristics Across Drug-Eluting and Bare-Metal Stent Trials

Trial Name	First Author	Stent	Mean Vessel Diameter, mm	MLD After Stent, mm	Mean Residual Stenosis, %	Diabetes Prevalence, %	Mean Lesion Length, mm
ASCENT	Baim	Palmaz-Schatz	2.95	...	10	20	11
		Multi-Link	2.96	...	8	19	10.9
BENESTENT	Serruys	Palmaz-Schatz	2.99	...	22	7	7.1
BENESTENT II	Serruys	Palmaz-Schatz (heparin-coated)	2.96	...	16	13	8.2
C-SIRIUS*	Schampaert	Bx Velocity	2.62	2.5	5.2	24	12.6
		Cypher (sirolimus-eluting)	2.65	2.53	6.1	24	14.5
DELIVER	Lansky	RX ML Penta	2.77	2.82	19.8	27	11.1
		RC ACHIEVE (paclitaxel-eluting)	2.85	2.86	19.1	31	11.7
ELUTES*	Gershlick	V-Flex Plus	2.99	2.68	10.5	10	10.8
		V-Flex Plus (paclitaxel-eluting 0.2 μg/mm^2)	3.03	2.78	9.6	22	11.3
		V-Flex Plus (paclitaxel-eluting 0.7 μg/mm^2)	2.9	2.63	10.6	15	10.6
		V-Flex Plus (paclitaxel-eluting 1.4 μg/mm^2)	2.93	2.72	8.1	21	10.2
		V-Flex Plus (paclitaxel-eluting 2.7 μg/mm^2)	2.95	2.66	10.1	11	11.1
E-SIRIUS	Schofer	Bx Velocity	2.51	2.38	6.6	27	15.1
		Cypher (sirolimus-eluting)	2.6	2.43	7.7	19	14.9
FUTURE I*	Grube	S-Stent	2.96	2.94	1.7	0	8.3
		S-Stent (everolimus-eluting)	3.1	3.07	1.8	4	9.2
GR-II	Lansky	GR-II	3.08	...	15.6	23	14.3
		Palmaz-Schatz	3.08	...	9.8	22	14
ISAR STEREO	Kastrati	ACS RX Multi-Link	3.1	...	2.7	17	13.9
		ACS RX Multi-Link Duet	3.1	...	4	19	13.8
NIRVANA	Baim	NIR	2.97	...	7	23	13.3
		Palmaz-Schatz	3.03	...	9	22	13.3
RAVEL	Morice	Bx Velocity	2.64	2.41	14	21	9.6
		Cypher (sirolimus-eluting)	2.6	2.43	11.9	16	9.6
SIRIUS	Moses	Bx Velocity	2.81	2.68	6	28	14.4
		Cypher (sirolimus-eluting)	2.79	2.67	5.4	25	14.4
STRESS	Fischman	Palmaz-Schatz	3.03	...	19	15	9.6
TAXUS II	Colombo	NIR	2.77	2.58	10.2	16	10.5
		NIR	2.73	2.52	12	14	10.7
		TAXUS (paclitaxel-eluting, slow release)	2.78	2.53	10.9	11	10.6
		TAXUS (paclitaxel-eluting, moderate release)	2.72	2.53	11	17	10.2
TAXUS IV	Stone	Express	2.75	2.67	4.9	25	13.4
		TAXUS (paclitaxel-eluting)	2.75	2.66	4.2	23	13.4
VISION	Kereiakes	Multi-Link Vision	2.92	...	...	23	10.6
Small-vessel trials							
	Park		2.55	2.44	4.2	13.1	...
ISAR-SMART	Kastrati	Multi-Link	2.41	2.35	7	25	12.5
BESMART	Koning	beStent Small	2.23	2.06	16	22	9.1
SISA	Doucet	beStent Artist	2.5	2.3	12.4	17.8	10.8
SISCA	Moer	beStent (heparin-coated)	2.44	2.22	11.3	12.2	...

*Trials with <50 subjects per arm.

generally expected with the comparison of continuous and binary variables measuring similar processes, late loss was consistently found to be a more efficient end point than binary angiographic restenosis across mean late loss, ranging from 0 to 1.0 mm (Figure 3). The largest difference in power between the 2 end points occurred at mean late loss levels of 0.1 to 0.7 mm.

Relationship of Late Loss to Binary Restenosis Rate

Using the relationship between the mean in-stent late loss and its SD defined above, one can predict the SD for a given hypothetical mean. We previously described a statistical method to overcome the greater degree of right skew in the late loss distribution at lower means by using a power

TABLE 2. Late Loss and Restenosis Rates Across Drug-Eluting and Bare-Metal Stent Trials

		Mean Late Loss, In-Stent, mm	In-Stent SD, mm	BAR, In-Stent, %	Mean Late Loss, In-Segment, mm	In-Segment SD, mm	BAR, In-Segment, %
ASCENT	Baim	0.91	0.57	22.1	...	...	...
		0.9	0.53	16	...	...	...
BENESTENT	Serruys	0.65	0.57	22	...	...	...
BENESTENT II	Serruys	0.8	0.54	16	...	...	...
C-SIRIUS*	Schampaert	1.02	0.69	45.5	0.79	0.74	52.3
		0.12	0.37	0	0.12	0.35	2.3
DELIVER	Lansky	0.98	0.57	20.6	0.56	0.59	22.4
		0.81	0.6	14.9	0.43	0.57	16.7
ELUTES*	Gershlick	0.73	0.73	20.6	...	...	...
		0.71	0.69	20.6	...	...	...
		0.47	0.64	14.3	...	...	...
		0.47	0.72	13.5	...	...	...
		0.11	0.5	3.2	...	...	...
E-SIRIUS	Schofer	1.05	0.61	41.7	0.8	0.57	42.9
		0.2	0.38	3.9	0.19	0.38	5.9
FUTURE I*	Grube	0.85	0.32	9.1	...	...	...
		0.11	0.23	0	...	...	...
GR-II	Lansky	1.21	0.69	47.3	...	...	...
		0.92	0.72	20.6	...	...	...
ISAR STEREO	Kastrati	0.94	0.74	15	...	...	...
		1.17	0.78	25.8	...	...	...
NIRVANA	Baim	0.8	0.61	19.3	...	...	...
		0.85	0.6	22.4	...	...	...
RAVEL	Morice	0.8	0.53	26.6	...	...	...
		−0.01	0.33	0	...	...	...
SIRIUS	Moses	1.0	0.7	35.4	0.81	0.67	36.3
		0.17	0.45	3.2	0.24	0.47	8.9
STRESS	Fischman	0.74	0.58	31.6	...	...	...
TAXUS II	Colombo	0.79	0.45	17.9	...	...	20.1
		0.77	0.5	20.2	...	...	23.8
		0.31	0.38	2.3	...	...	...
		0.3	0.39	4.7	...	...	...
TAXUS IV	Stone	0.92	0.58	24.4	0.61	0.57	26.6
		0.39	0.5	5.5	0.23	0.44	7.9
VISION	Kereiakes	0.83	0.56	15.7	...	...	...
Small-vessel trials							
	Park	1.12	0.67	35.7	...	...	...
ISAR-SMART	Kastrati	1.04	0.73	35.7	...	...	...
BESMART	Koning	0.65	0.58	21	...	...	...
SISA	Doucet	0.54	0.48	9.7	...	...	...
SISCA	Moer	0.89	0.52	28	...	...	...

BAR indicates binary angiographic restenosis.
*Trials with <50 subjects per arm.

transformation varying with the mean late loss.[13] Combination of these 2 methods yields a model to predict binary angiographic restenosis rates from late loss for a study population of any given reference vessel diameter and residual stenosis (Table 3).[37] This model describes a monotonic and curvilinear relationship between mean late loss and restenosis rate (Figure 4). The expected incremental restenosis rate between 2 mean late losses of 0.2 and 0.4 mm is 3.1%, whereas the incremental restenosis rate between 2 mean late losses of 0.4 and 0.6 mm is 6.4% in a reference population

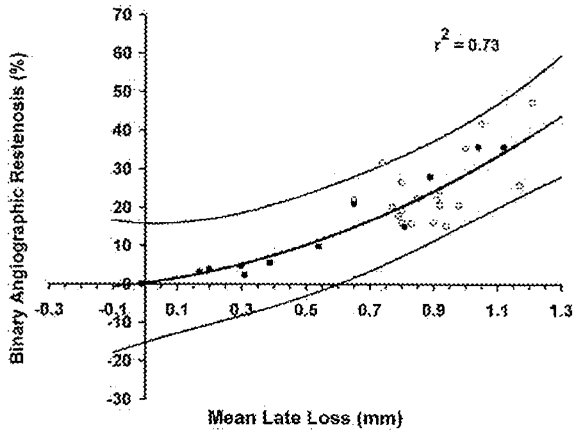

Figure 1. In-stent late loss: mean vs binary angiographic restenosis rate. Open circles represent bare-metal stent treatments in vessels >2.5 mm in diameter, squares represent bare-metal stent treatments in small vessels (≤2.5 mm), and filled circles represent drug-eluting stent treatments. Each data point represents a trial arm with a minimum of 50 subjects. The bold line represents the fitted relationship, and the thin lines represent 95% confidence bounds for this fitted line.

with mean reference vessel diameter of 2.79 mm and residual stenosis of 6% (Table 3).

Discussion

The success of drug-eluting stents has changed expectations of coronary stent performance. Standard clinical binary end points have become difficult to use as the only measures of restenosis in the clinical studies necessary for the evaluation of new drug-eluting stents. Binary angiographic restenosis and clinical revascularization of the target lesion or vessel now occur too infrequently to provide stable estimates for either single-arm studies or adequate contrast of restenosis rates between competing drug-eluting stent systems for randomized trials. Small- to moderate-sized trials of new drug-stent combinations or new drug-dose formulations cannot be performed with efficiency with the use of traditional binary outcomes that require a minimum of 1000 evaluable patients per arm to enclose a restenosis rate of 6% within a 3% 95% CI. To prevent unnecessary exposure to ineffective therapies, a need for more powerful end points of restenosis has emerged.

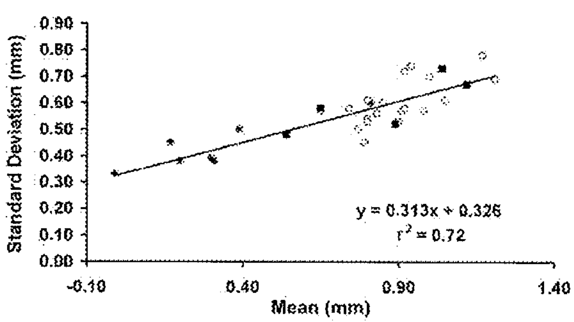

Figure 2. In-stent late loss: mean vs SD. Open circles represent bare-metal stent treatments in vessels >2.5 mm in diameter, squares represent bare-metal stent treatments in small vessels (≤2.5 mm), and filled circles represent drug-eluting stent treatments. Each data point represents a trial arm with a minimum of 50 subjects.

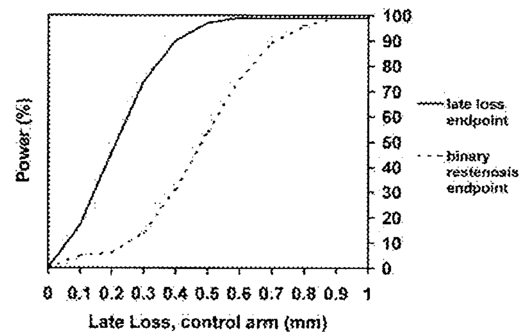

Figure 3. Power curves for in-stent late loss and binary angiographic restenosis (BAR). Shown is mean late loss vs power to detect a 35% treatment effect if late loss is used (straight line) and if binary restenosis rate is used (dotted line) in a hypothetical randomized trial of 2 stents with 200 subjects per arm.

We sought to evaluate the generalizability and power of the angiographic end point late loss as a summary statistic for study samples. We demonstrated that across the published stent trials, a strong positive association exists between the mean in-stent late loss estimates and binary angiographic restenosis rates. Specifically, over the range of trials observing late loss from 0 to 1.3 mm, higher sample mean late losses were associated with higher sample restenosis rates. Consequently, the conditions for a paradoxical result in which an increasing increment of late loss might correspond to a decreasing increment of binary restenosis risk did not exist. Further statistical support for this positive monotonic (nondecreasing) correlation was the association of late loss sample mean and SD. The theoretical possibility that an increasing

TABLE 3. Prediction of Binary Angiographic Restenosis Rate From Mean In-Stent Late Loss

Mean Late Loss, mm	Predicted SD, mm	BAR (Normal Method)	Optimum Power	BAR (Transformed Method)
0	0.33	0.0	0.0	0.4
0.1	0.36	0.1	0.1	0.8
0.2	0.39	0.3	0.2	1.5
0.3	0.42	1.0	0.3	2.7
0.4	0.45	2.6	0.4	4.6
0.5	0.48	5.4	0.5	7.3
0.6	0.51	9.4	0.6	11.0
0.7	0.55	14.6	0.7	15.6
0.8	0.58	20.5	0.8	21.0
0.9	0.61	26.9	0.9	27.0
1	0.64	33.3	1.0	33.3

BAR indicates binary angiographic restenosis. Predicted SD is based on regression (SD=0.33+0.31×late loss); predicted restenosis rate is based on normality of power-transformed late loss and delta method approximation of variance.[37] In this example mean reference vessel diameter was assumed to be 2.79 mm, and mean poststent MLD was assumed to be 2.67 mm.

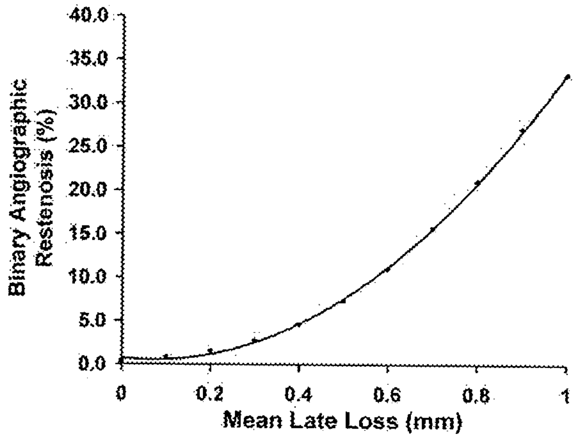

Figure 4. Mean late loss vs predicted restenosis rate. Shown are predicted restenosis rates for a reference population of mean reference vessel diameter 2.79 mm and mean poststent MLD 2.67 mm.

increment of mean late loss could correspond to a decreasing increment of SD, and thus paradoxically lower restenosis risk, was also not demonstrated in the empirical observations of trials reporting late loss to date.

The utility of late loss as a measure of restenosis in clinical trials is supported by the following observations. First, if a uniform stent diameter at deployment is assumed, late loss is a consistent measure of the magnitude of the renarrowing process. Although it is estimated from 2 angiograms, usually separated over a 6- to 9-month period, the estimates have shown a consistency of correlation between its value and restenosis rate (Figure 1). Because the renarrowing process within a stent is due solely to the hyperplastic component, with no contribution from the vascular contraction component seen in nonstent procedures, late loss is an intuitive measure of neointimal hyperplasia, the pathological target of drug-eluting stents.[11]

Second, late loss is a powerful measure of binary restenosis proclivity. The predictable monotonic relationship of late loss to restenosis allows estimation of restenosis probability in a given study population with known reference vessel diameter and poststent MLD. Observed results (Figure 1) and our model (Figure 4) both show substantial increased risk of binary angiographic restenosis when observed mean late loss increases over the range of 0.1- to 0.7-mm mean in-stent late loss. This generalized model of late loss is not a regression of late loss on binary restenosis but rather an empirical model relating mean values of late loss to their predictable distributions. Thus, the curvilinear predictive model, based on expected late loss probability densities, is similar in shape to the observed data.

Additionally, when late loss is expected to range from 0.1 to 0.7 mm, as in trials designed to compare new drug-eluting stents, late loss has greater power than binary angiographic restenosis to discriminate restenosis tendency for moderate-sized (≈200 subjects) trials (Figure 3) and even more so for smaller sample sizes. Although larger pivotal trials (of ≳1500 subjects) would be required to power dichotomous end points such as target vessel failure, the confidence bounds of the late loss estimate are narrower than those of the binary angiographic restenosis end points at any sample size.

If there is substantial tapering of a vessel over the length of the analysis segment, then the true magnitude of neointimal hyperplasia may be underestimated by late loss. This is a particular problem for the "in-segment" measurement of late loss in which subtraction of the MLD obtained from the 5-mm "step-up" and "step-down" shoulders may systematically underestimate the amount of neointimal hyperplasia compared with the in-stent measurement. If there were significant poststent variability of MLD along the length of the stent, then the same limitation would be true for the in-stent measurement. In the present stenting trials with an average residual stenosis of 5%, however, the residual diameter is relatively uniform throughout the stent (ie, with little tapering of the stent itself); therefore, most variability in the in-stent late loss measurement is created by variations in the MLD at late follow-up, not after the procedure.

Late Loss and Clinical Trials of Drug-Eluting Stents

New drug-eluting stents are best evaluated by execution of 1 or 2 large "pivotal" randomized trials in which comparison is made to an accepted standard. Pivotal trials seek to estimate efficacy (freedom from restenosis) and detect important rare serious adverse events, such as coronary thrombosis or aneurysm formation. End points that combine safety and efficacy measures, such as target vessel failure or major adverse cardiac events (both of which include death, myocardial infarction, and clinically driven repeated coronary revascularization), have been deemed to be the most inclusive and remain important for pivotal stent trials. Large sample sizes (generally >1000 to 2000 subjects) are required for contrasting target vessel failure rates between the competing randomized arms, expected to range from 5% to 15%. In smaller pilot, nonpivotal, or follow-up trials, these end points lose power. The strong positive correlation and generalized monotonic relationship between late loss and restenosis, combined with its high statistical power, make late loss an attractive end point for nonpivotal drug-eluting stent trials.

We have estimated that even small differences in mean in-stent late loss can translate to important differences in binary restenosis (Table 3, Figure 4). Small differences in clinical restenosis are important for several reasons. First, cost-effectiveness analysis suggests that small differences in restenosis rates can translate to meaningful differences in cost.[32] Second, the small differences in restenosis risk seen in pivotal study populations are likely amplified in practice, where the magnitude of clinical benefit is expected to increase with the risk profile of the target patient population.[34,35] Regardless of the actual (and currently unknown) threshold of late loss difference that is clinically relevant, increasing values of late loss are associated with increasing risk of binary restenosis. These findings support the notion that late loss performance can reliably predict the restenosis propensity for new drug-eluting stents.

Limitations

We chose binary angiographic restenosis as the outcome variable used to validate late loss. Our choice of angiographic binary restenosis was based on the wide availability of this standard variable in the literature and the lack of a consistently reported clinical restenosis end point. Although the 50% diameter stenosis cutoff definition of binary angiographic restenosis may not define all patients with physiological coronary flow obstruction, it is a robust measure of clinical restenosis, with high correlation between binary angiographic restenosis and target lesion or target vessel revascularization.[36] Finally, the end point percent diameter stenosis is an excellent measure of the final follow-up result in a given patient. However, percent diameter stenosis has a wide range (eg, 15% to 35% for percent diameter stenosis versus 0 to 1.0 for late loss), and its calculation and interpretation are dependent on reference vessel size, making its use in nonrandomized comparisons more problematic than that of late loss.

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Interventional Cardiology

Relationship of Late Loss in Lumen Diameter to Coronary Restenosis in Sirolimus-Eluting Stents

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Background—Observed rates of restenosis after drug-eluting stenting are low (<10%). Identification of a reliable and powerful angiographic end point will be useful in future trials.

Methods and Results—Late loss (postprocedural minimum lumen diameter minus 8-month minimum lumen diameter) was measured in the angiographic cohorts of the SIRIUS (n=703) and E-SIRIUS (n=308) trials. Two techniques, the standard normal approximation and an optimized power transformation, were used to predict binary angiographic restenosis rates and compare them with observed restenosis rates. The mean in-stent late loss observed in the SIRIUS trial was 0.17±0.45 mm (sirolimus) versus 1.00±0.70 mm (control). If a normal distribution was assumed, late loss accurately estimated in-stent binary angiographic restenosis for the control arm (predicted 35.4% versus observed 35.4%) but underestimated it in the sirolimus arm (predicted 0.6% versus observed 3.2%). Power transformation improved the reliability of the estimate in the sirolimus arm (predicted 3.2% [CI 1.0% to 6.7%]) with similar improvements in the E-SIRIUS trial (predicted 4.0% [CI 1.2% to 7.0%] versus observed 3.9%). In the sirolimus-eluting stent arm, in-stent late loss correlated better with target-lesion revascularization than in-segment late loss (c-statistic=0.915 versus 0.665).

Conclusions—Because distributions of late loss with a low mean are right-skewed, the use of a transformation improves the accuracy of predicting low binary restenosis rates. Late loss is monotonically correlated with the probability of restenosis and yields a more efficient estimate of the restenosis process in the era of lower binary restenosis rates. (***Circulation*. 2005;111:321-327.**)

Key Words: angioplasty ■ stents ■ restenosis

The evaluation of percutaneous coronary devices over the past 20 years has relied on an estimation of cumulative late-term failure, manifested largely by recurrent renarrowing of the treated coronary segment.[1] A variety of continuous end points, including the minimum lumen diameter (MLD) or percent diameter stenosis at 6 to 9 months after intervention, precisely describe the stable long-term result on the treated coronary segment.[2] Binary end points that classify a treatment as ultimately successful or unsuccessful, such as binary angiographic restenosis (BAR) or target-lesion revascularization (TLR), are more commonly compared across competing coronary treatments. Although BAR is merely the frequency of percent diameter stenosis greater than an arbitrary threshold of 50% and is itself poorly correlated with the need for repeat intervention for any given subject,[3] its rate in trials has been highly correlated with the rate of TLR.[4] The moderately high rates of BAR and TLR seen in conventional trials (15% to 40%) have provided enough power for adequate discrimination between competing percutaneous therapies enrolling ≈1000 subjects.[5-9]

In contrast, several recent drug-eluting stent (DES) trials have demonstrated a breakthrough in the reduction of late restenosis compared with bare metal stents, with a consistent incidence of BAR and TLR below 10%.[10,11] Even with the achieved low rates, which may underestimate the rate in actual practice or in high-risk groups,[12-17] cost-effectiveness analysis provides economic and quality-of-life incentives to distinguish therapies with restenosis rates below 10%.[18] However, the statistical power available to determine superiority (or demonstrate noninferiority) in competing DES treatments is markedly reduced when sample sizes of 2000 subjects or less are used. A reevaluation of continuous

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restenosis metrics as discriminators between competing DES therapies is necessary, especially for underpowered pilot (50 to 150 subjects) and pivotal (≈1000 subjects) trials. The traditional angiographic variables, late MLD and percent diameter stenosis, are powerful continuous measures, but late loss (postprocedural MLD minus 8-month MLD) has the unique ability to distinguish the magnitude of late intimal renarrowing from baseline and procedural variables (reference vessel diameter and residual stenosis). We sought to evaluate the reliability of late loss in providing a monotonic (nondecreasing) metric of antirestenosis effect and its ability to predict relative measures of restenosis in the DES era.

Methods

Study Population

Primary data were analyzed from the SIRIUS (Sirolimus-Eluting Bx VELOCITY Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) and E-SIRUS (European Sirolimus-Eluting Bx VELOCITY Balloon-Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions) randomized trials.[10,19] The SIRIUS trial was a 1101-patient, multicenter, randomized, double-blind evaluation of the sirolimus-eluting Bx Velocity stent compared with the standard Bx Velocity stent. Patients with a de novo coronary artery stenosis 15 to 30 mm in length in a 2.5- to 3.5-mm diameter vessel were eligible. E-SIRIUS was a 353-patient, multicenter, randomized trial of the same active and control stent arms, performed in Europe. Patients with a de novo coronary artery stenosis 15 to 32 mm in length in a 2.5- to 3.0-mm diameter vessel were eligible. Other clinical inclusion and exclusion criteria were similar to the SIRIUS trial. All investigational sites received approval from their local hospital institutional review boards.

The first 850 patient observations from the SIRIUS trial, the 8-month angiographic follow-up cohort, were used to develop the late-loss models (prediction cohort; complete follow-up in 703 patients). The 353-patient E-SIRIUS trial required 8-month follow-up in all subjects (completed in 308 subjects) and was used as the test cohort for the late-loss models generated from the SIRIUS study. Further predictions of relative restenosis based on late-loss estimates were made for the TAXUS (TAXUS Express Paclitaxel-Eluting Stent for Treatment of De Novo Lesions) IV trial.[11]

Angiographic Analysis

Standard image acquisition was performed at the clinical sites as described previously.[10,19] Cineangiograms for both trials were forwarded to the Brigham and Women's Hospital Angiographic Core Laboratory for review by observers blinded to the treatment assignment.

All procedural and follow-up angiograms were reviewed with standard morphological criteria.[20–22] Quantitative angiographic analysis was performed with a validated automated edge-detection algorithm (Medis CMS).[23] A 5-mm segment of reference diameter proximal and distal to the stenosis was used to calculate the average reference vessel diameter. MLDs were measured within the stent (in-stent analysis) and within the segment including 5 mm proximal and distal to the stent margins (in-segment analysis).[23a]

Definitions

Late loss was defined as the MLD immediately after the procedure minus the MLD at 8-month follow-up. Percent diameter stenosis was defined as [1−(MLD/reference vessel diameter)×100]. BAR was defined as a >50% diameter stenosis at follow-up. Lesion length was defined as the axial extent of the lesion that contained a shoulder-to-shoulder lumen reduction by ≥20%. TLR was defined as clinically driven revascularization of the target lesion by 9 months of follow-up and was adjudicated by an independent Clinical Events Committee.

Statistical Analysis

Ordinal variables are expressed as frequencies, and continuous variables are expressed as mean±SD. Binary variables were compared with χ^2 analysis, and continuous variables were evaluated with the Student's t test. A 2-sided probability value ≤0.05 was considered significant. Statistical analyses were performed in SAS (version 8.2) unless otherwise noted.

Prediction of Angiographic Restenosis Rate From Late Loss

The normality of the distributions of late loss (in-stent and in-segment) were tested in each arm (active and control) of the SIRIUS trial with the Kolmogorov-Smirnov test. The fit of other parametric distributions (Gamma, Weibull) and the following transformations of late loss were examined systematically: log, square root, log normal, log-logistic, and power. The power-transformation procedure was the most flexible in transforming the late-loss distribution. The BOXCOX procedure (STATA) was used to screen the fit of the power transformation, then the optimum power (ranging from 0 to 1) was selected to predict the BAR rate observed in each arm of the SIRIUS trial (prediction cohort). The new transformed mean and SD were computed to correct for the rightward skew of the data (see online-only Data Supplement Appendix).

Predicted BAR rates were computed for the standard (normal assumption with the expected value of late loss required to result in a >50% diameter stenosis) and transformed methods and compared with the observed BAR rates for SIRIUS and E-SIRIUS (the test cohort) trials. Confidence intervals (2-sided, 95%) were obtained by simulating 1000 bootstrap samples.[24] Percent error was defined as 100 times the difference between the observed rate and the predicted rate divided by the observed rate. Finally, we applied a simple interpolation of the published in-stent late-loss result in the active arm of the TAXUS IV trial[11] between the active and control arms of the SIRIUS trial to yield a power-transformation value for TAXUS IV.

Correlation of Late Loss With Clinical Restenosis

The ability of late loss to predict clinical restenosis in the SIRIUS trial was examined with logistic regression models of TLR as the outcome variable and either in-stent or in-segment late loss as the dependent variable. The c-statistic was measured and compared for each (1.0 signifying perfect accuracy).

Results

Lesion Characteristics

The angiographic characteristics of the lesions are listed in Table 1, which demonstrates highly significant ($P<0.001$) differences in late loss between the randomized arms for the SIRIUS and E-SIRIUS trials for both in-segment and in-stent late-loss measurements. The control-arm in-segment late-loss means (0.81 mm SIRIUS, 0.80 mm E-SIRIUS) were lower than the in-stent late-loss means (1.00 and 1.05 mm, respectively). The active-arm in-segment late-loss mean was higher than the in-stent mean for the SIRIUS trial (0.24 versus 0.17 mm) but similar in the E-SIRIUS trial (0.19 versus 0.20 mm).

Late Loss Is Not Normally Distributed

The distribution of both in-stent and in-segment late loss was not normal for either arm of the trial (in-segment late loss: $P<0.01$ sirolimus, $P<0.01$ control; in-stent late loss: $P<0.01$ sirolimus, $P=0.047$ control), and the magnitude of right skewness (from a normal distribution where skew=0) was greatest in the sirolimus arm (in-segment late-loss skewness: 0.89 sirolimus, 0.43 control, in-stent: 1.23 sirolimus, 0.32 control; Figures 1 and 2).

TABLE 1. Angiographic Characteristics of SIRIUS and E-SIRIUS Trials

Variable	Sirolimus	Control	*P*
SIRIUS trial			
Reference vessel diameter, mm	2.79±0.45	2.82±0.49	0.43
MLD, mm	0.97±0.40	0.98±0.39	0.72
In-stent			
Final MLD, mm	2.68±0.41	2.68±0.41	0.94
Follow-up MLD, mm	2.50±0.58	1.69±0.79	<0.001
Late loss, mm	0.17±0.44	1.00±0.70	<0.001
BAR, %	3.2	35.4	<0.001
In-segment			
Final MLD, mm	2.39±0.46	2.40±0.44	0.83
Follow-up MLD, mm	2.15±0.61	1.60±0.72	<0.001
Late loss, mm	0.24±0.47	0.81±0.67	<0.001
BAR, %	8.9	36.3	<0.001
E-SIRIUS trial			
Reference vessel diameter, mm	2.60±0.37	2.51±0.37	0.025
MLD, mm	0.90±0.30	0.85±0.31	0.13
In-stent			
Final MLD, mm	2.43±0.31	2.38±0.33	0.15
Follow-up MLD, mm	2.22±0.48	1.33±0.63	<0.001
Late loss, mm	0.20±0.38	1.05±0.61	<0.001
BAR, %	3.9	41.7	<0.001
In-segment			
Final MLD, mm	2.17±0.39	2.10±0.39	0.10
Follow-up MLD, mm	1.97±0.48	1.29±0.61	<0.001
Late loss, mm	0.19±0.38	0.80±0.57	<0.001
BAR, %	5.9	42.3	<0.001

Power transformation of in-stent late loss is the optimum method to predict BAR rates from mean late loss.

Compared with other transformations and nonnormal distributions, the 0.13 power transformation, ie, $(\text{late loss})^{0.13}$, was the optimum for restoring normality of the right tail of in-segment late loss in the active arm, and the 0.52 power transformation, ie, $(\text{late loss})^{0.52}$, was the optimum for the control arm. For in-stent late loss, the optimum powers were 0.13 for the active arm and 0.99 for the control arm. The in-segment and in-stent late-loss power transformations were then applied to predict BAR rates. The transformed and nontransformed predictions for both SIRIUS (prediction set) and E-SIRIUS (test set) were compared with the observed rates (Table 2).

Predictions based on the normal assumption underestimated restenosis rates in the active arms of SIRIUS and E-SIRIUS trials because of the lack of compensation for right-skewed late-loss distributions. For the SIRIUS trial, the active arm in-stent binary restenosis rate was underestimated by 81% (0.6% predicted rate compared with 3.2% observed rate), and the active in-segment binary restenosis rate was underestimated by 38% (5.5% predicted rate compared with 8.9% observed rate). Similarly, in the test cohort (E-SIRIUS), the transformed active-arm predictions matched better with the observed rates (Table 2). Transformed in-stent late loss

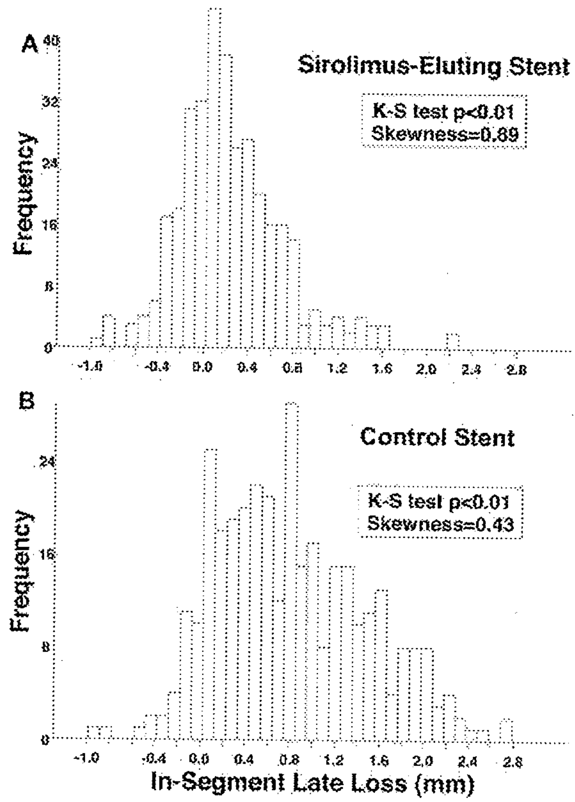

Figure 1. Distribution of in-segment late loss. A, Sirolimus arm. B, Control arm. K-S test indicates Kolmogorov-Smirnov.

was the most predictive of the E-SIRIUS observed BAR rates compared with in-segment transformed late loss and both in-stent and in-segment nontransformed late loss.

In-Stent Late Loss Is Correlated With TLR

We compared predictive models of TLR using in-stent and in-segment late loss. In the active arm, in-stent late loss was a more reliable predictor of TLR (c-statistic 0.915, versus 0.665 for in-segment), whereas TLR from the control arm was similarly predicted from in-stent or in-segment late loss (c-statistic 0.897 versus 0.916, respectively).

Predicting Restenosis Rates for Other DES Systems With In-Stent Late Loss

The optimum transformation power for prediction of BAR from late loss depends on the mean late loss, which varied from 0.13 mm in the active SIRIUS arm to 0.99 mm in the control arm. Interpolation of an in-stent late loss of 0.39 mm observed in the active arm of the TAXUS IV trial[11] yielded a power-transformation parameter of 0.36. The published mean reference vessel diameter of 2.75 mm and postprocedural MLD of 2.66 mm in-stent were then used to predict the in-stent BAR rate. With the in-stent late-loss normal approximation (standard method), the predicted in-stent BAR was 3.7%, an underestimate of 39% compared with the observed in-stent BAR rate of 5.5%. The in-stent late-loss transforma-

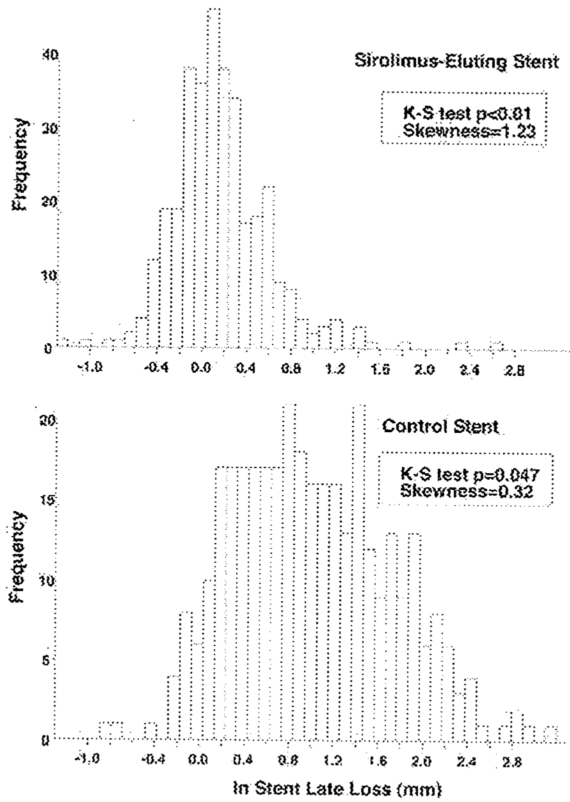

Figure 2. Distribution of in-stent late loss. A, Sirolimus arm. B, Control arm. K-S test indicates Kolmogorov-Smirnov.

tion approximation, on the other hand, predicted an in-stent BAR rate of 6.1%, an overestimate of only 10% (Figure 3).

Discussion

Percutaneous coronary therapies have generally been compared on the basis of their restenosis propensities.[25] BAR rates and TLR rates ranging between 15% and 25% for stents and between 20% and 40% for other angioplasty devices[5–8] allowed detection of modest differences in restenosis rates in clinical trials of fewer than 1000 subjects.[26,27]

The evaluation of restenosis in the DES era is more complex. In the SIRIUS and TAXUS experience, binary angiographic and clinical restenosis rates are below 10%,[10,11] which makes comparisons between competing DES treatments more difficult with sample sizes below 1000 to 2000 subjects. Moreover, the initial evaluation of future candidate DES will likely rely on smaller dose-finding studies of fewer than 100 subjects per test group, in which the infrequent binary restenosis end points will be too insensitive to be effective discriminators.

In the present study, we have evaluated late loss as a potential gauge of restenosis in the DES era. First, in the DES era, in which mean late loss is often a fraction of its SD, right skewness can be overcome with power transformation to allow accurate approximation of BAR rates. Second, late loss is correlated with restenosis: The models in the present study show a monotonic (nondecreasing) relationship between higher late loss and higher restenosis rates in the 2 SIRIUS trials studied, as well as the indirect prediction of the TAXUS IV restenosis rate. Third, in-stent late loss showed a better correlation with TLR than in-segment late loss for the DESs studied. With these robust features, in-stent late loss is a sensitive indicator of restenosis propensity.

Late loss was initially developed as a tool to compare the mechanisms of restenosis between different coronary interventions such as balloon angioplasty, stenting, and atherectomy.[28] Within stents, late loss is an absolute measure of neointimal renarrowing, with vascular contraction being prevented by the stent framework.[29,30] In-stent neointimal renarrowing, however, is still only 1 factor that determines the probability of restenosis, which is also influenced by the vessel diameter. Commonly reported measures of relative restenosis include percent diameter stenosis and BAR rates. In the pre-DES era, among coronary devices, stents had the lowest relative restenosis but, paradoxically, also had the highest late loss.[25] As a result, comparisons of different mechanical percutaneous interventions (angioplasty, stents, atherectomy) relied on relative measures of restenosis. In the case of similar mechanical interventions, however, such as stents with similar acute gains, the need for relative adjustments is reduced, and late loss may be a valuable tool to gauge antirestenosis effect.

Late Loss and Its Skewed Distribution for DESs

With bare metal stenting, late loss has been observed to follow a near-normal distribution.[1,31] Bare metal stent trials and registries have demonstrated mean late losses varying from 0.6 to 1.2 mm.[5,6,26,27,32–35] The RAVEL trial of the sirolimus-eluting Bx Velocity stent was the first randomized trial to report a stent with an average late loss well below the expected historical range, as well as its own control arm (in-stent late loss −0.01 mm active versus 0.80 mm control), which corresponded to a BAR rate of 0% for the active arm versus 26% in the control arm.[36]

As the positive mean of any normal distribution is reduced enough so that its spread becomes significantly bounded by zero, it becomes right-skewed. The distribution of late loss for bare metal stents is only marginally skewed by zero. In the case of the sirolimus-eluting stent, however, for which the mean late loss has ranged between −0.01 and 0.24 mm, the late-loss distributions studied are markedly deviated from normal and skewed to the right. In such skewed distributions, the variance, as estimated from the sample SD, no longer accurately denotes the deviation from the mean. If the calculated SD is used to predict binary event rates in this right tail, the predicted binary rates will be underestimated (Figure 4). To accurately study the behavior of such a distribution, either transformation or selection of a distribution that more closely resembles the skewed data becomes necessary rather than reliance on traditional normal methods. The power transformation used in the present study restored a more predictable normal distribution and demonstrated a monotonic relationship between late loss and restenosis.

In-Stent Versus In-Segment Late Loss

Whereas in-stent measurements of follow-up MLD have been relied on for the evaluation of virtually all bare metal stents to

TABLE 2. Prediction of BAR

	Observed Late Loss, mm Mean	SD	Observed BAR, %	Predicted BAR, %, Normal Assumption (95% CI)	Predicted BAR, %, Power-Transformed Method (95% CI)
In-segment BAR from in-segment late loss					
SIRIUS					
Control	0.81	0.67	36.3	39.3 (35.1–43.9)	36.3 (32.5–40.3)
Sirolimus	0.24	0.47	8.9	5.5 (3.0–8.0)	8.9 (6.1–11.9)
E-SIRIUS					
Control	0.80	0.57	42.3	47.7 (41.2–53.6)	44.1 (37.9–50.4)
Sirolimus	0.19	0.38	5.9	4.8 (1.4–10.5)	8.5 (4.2–12.8)
In-stent BAR from in-stent late loss					
SIRIUS					
Control	1.00	0.70	35.4	35.4 (30.9–39.5)	35.4 (31.3–39.3)
Sirolimus	0.17	0.44	3.2	0.6 (0.15–1.6)	3.2 (1.0–6.7)
E-SIRIUS					
Control	1.05	0.61	41.7	45.8 (39.7–51.3)	45.7 (39.2–51.9)
Sirolimus	0.20	0.38	3.9	1.2 (0.05–4.3)	4.0 (1.2–7.0)

Note that power-transformation methods were developed on the basis of the SIRIUS trial results (prediction cohort) and tested in the E-SIRIUS trial (test cohort).

date,[5,6,37] the observation of an exuberant renarrowing at the margins of stents, despite a therapeutic effect within the stent observed in early brachytherapy trials[38] and some pilot DES trials,[39] termed "edge effect" or "candy-wrapper restenosis," led to inclusion of the zones proximal and distal to the stent for analysis. When the binary variable angiographic restenosis is used, the more inclusive in-segment analysis has the attractive ability to capture events that occur only at the edges, whereas the in-stent analysis does not.

In the present examination of late loss, we also sought to determine whether the in-stent or in-segment analysis was more reliable. We found that for the control arm, in-stent and in-segment analyses were essentially equivalent, with similar c-statistics for predicting TLR. However, in the sirolimus-eluting stent arm, in-stent late loss was much better correlated with TLR than was in-segment late loss.

Ideally, an angiographic measure of neointimal renarrowing would represent the magnitude of maximum change in lumen diameter from the time of stenting to the follow up angiogram across the treatment site and margins. Such a measurement would require a comparison across the 2 time points slice by slice along the length of the vessel, within matched, fine ($\approx$1 mm) increments. Practically, however, standard techniques of measuring late loss have compared MLDs from a specified zone. The in-stent late-loss calculation compares MLDs both from within the stented zone. The in-segment late-loss calculation compares the minimum of the proximal, distal, and stent zone diameters (in-segment MLD) after stenting and at late follow-up, rather than the maximum late loss from these zones. Thus, the in-segment calculation has the possibility of comparing different regions rather than representing the maximum late loss from among the zones evaluated. Because the greatest acute gain and late loss are usually within the stented zone, the in-segment postprocedural MLD will tend to be measured outside of the stented zone and the follow-up MLD within the stented zone, such that in-segment late loss will necessarily underestimate the maximum late loss (within the stent). In the absence of an edge effect,[10,19,36] it is not surprising that the in-stent late-loss measurement best reflects the likelihood of clinical restenosis. The difference in c-statistics for in-stent compared with in-segment late loss reflects the better correlation of in-stent late loss with the probability of TLR when sirolimus-eluting stents are used.

Other Continuous Absolute and Relative Angiographic End Points

Two other angiographic variables should be considered as alternatives: an absolute measure of restenosis, late MLD, and a relative measure of restenosis, late percent diameter stenosis. These continuous measures are correlated with restenosis. The unique advantage of late loss is the ability to distinguish the magnitude of late intimal renarrowing from baseline and procedural variables such as reference vessel diameter and residual stenosis. Whereas percent diameter stenosis is directly linked to the likelihood of target-vessel revascularization in a given patient, late loss isolates the neointimal hyperplasia component of the restenosis process for a given DES.

Clinical Implications for In-Stent Late Loss

Proper binary restenosis rate estimation from late loss requires mathematical transformation of the data, because traditional extrapolation will diminish the actual differences in binary restenosis rates for any 2 comparable values of late loss. This underestimation error is most pronounced at low restenosis rates where current DES clinical trials range. This

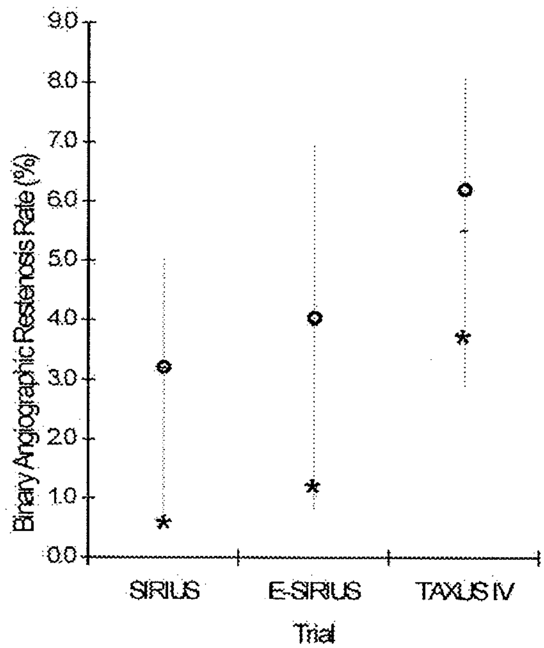

Figure 3. Comparison of observed BAR rates with predicted rates from in-stent late loss using either normal method or power-transformed method across several published DES trials. When BAR rates <10% are observed in DES arms, normal method underestimates restenosis rates, and power-transformed method is closer to observed rates. Symbol - represents observed rate of BAR, and straight lines represent 95% CIs for this rate. Symbols ° and * represent predicted rates from power-transformed and normal methods, respectively.

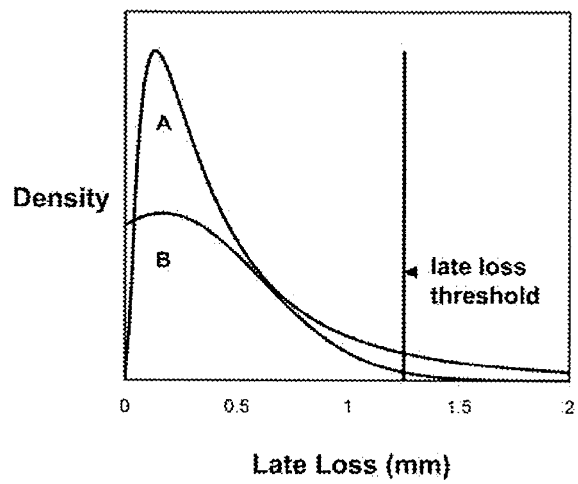

Figure 4. Density function of late loss. Assumed normal distribution (A) vs right-skewed distribution (B). By calculating late loss over which >50% diameter stenosis would be present [late-loss threshold=0.5(RVD)−(RVD−postprocedural MLD)], where RVD indicates reference vessel diameter, rate of BAR may be estimated from mean late loss (BAR=area under curve A or B beyond threshold). When mean late loss is small or BAR rates are low (<10%), estimation with normal distribution assumption underestimates rate of binary restenosis compared with modeling that takes right-skewed distribution of late loss into account.

method of transformation will require future validation as additional DES studies are published. Although higher late-loss values correlate positively with higher restenosis rates, to what extent small differences in late loss are clinically meaningful between comparative DES systems may be more difficult to answer. These small differences may have the most important effects in high-restenosis-risk groups.

Study Limitations

Although vessel diameter may have a smaller effect on late loss than on relative measures of restenosis, such as other restenosis end points, late loss is best used to compare stents between groups that have similar acute gain, lesion lengths, and diabetes prevalence, as in a randomized, controlled trial. Finally, although in-stent late loss was most reliable for prediction of angiographic and clinical restenosis in sirolimus-eluting stents, analysis of the proximal and distal zones is still mandatory to detect edge effects when new DESs are studied.

Conclusions

Late loss is a robust end point that may be used in future trials to discriminate between new DESs for which binary rates are anticipated to be low. An angiographic surrogate for neointimal hyperplasia, in-stent late loss is positively correlated with other measures of relative restenosis and clinical restenosis and may be useful, particularly in early trials in which sample size is limited.

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Robustness of Late Lumen Loss in Discriminating Drug-Eluting Stents Across Variable Observational and Randomized Trials

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Background**—**Binary angiographic and clinical restenosis rates can vary widely between clinical studies, even for the same stent, influenced heavily by case-mix covariates that differ among observational and randomized trials intended to assess a given stent system. We hypothesized that mean in-stent late loss might be a more stable estimator of restenosis propensity across such studies.

Methods and Results**—**In 46 trials of drug-eluting and bare-metal stenting, increasing mean late loss was associated with higher target lesion revascularization (TLR) rates ($P<0.001$). When the class of bare-metal stents was compared with the class of effective drug-eluting stents, late loss was more discriminating than TLR as measured by the high intraclass correlation coefficient (ρ) (late loss, $\rho=0.71$ versus TLR, $\rho=0.22$; 95% CI of difference=0.33, 0.65). When the individual drug-eluting stents and bare-metal stents were compared, late loss was a better discriminator than TLR (0.68 versus 0.19; 95% CI of difference=0.24, 0.60). Greater adjustments of study covariates are needed to stabilize assessments of TLR compared with late loss because of greater influence of reference vessel diameter on TLR than on in-stent late loss. Optimization of late loss with the use of a novel method of standardization according to diabetes prevalence and mean lesion length resulted in minor adjustments in late loss (<0.08 mm for 90% of reported trials) and an ordered array of mean late loss values for the stent systems studied.

Conclusions**—**Late loss is more reliable than restenosis rates for discriminating restenosis propensity between new drug-eluting stent platforms across studies and might be the optimum end point for evaluating drug-eluting stents in early, nonrandomized studies. **(*Circulation.* 2005;112:2833-2839.)**

Key Words: angioplasty ■ coronary disease ■ restenosis ■ stents ■ trials

Rates of restenosis after stenting of coronary artery obstructions vary widely depending on the prevalence of known and unknown predictors of restenosis.[1] Some bare-metal stent registries have shown clinical restenosis rates of <5%,[2,3] on a par with rates observed recently in drug-eluting stents.[4,5] However, these low rates of restenosis for bare-metal stents are attributable to the lower risk of the populations in which they were tested rather than to a lower restenosis propensity of bare-metal stents. When tested across broad ranges of risk, the same stent may be observed to have restenosis rates that vary by as much as 4-fold.[3,6] Clinical restenosis rates therefore do not allow objective comparison of the restenosis propensity across randomized or observational studies.

Late lumen loss, defined as the difference between the minimum lumen diameter (MLD) immediately after stenting and the MLD at 6-to 8-month follow-up, has been used in pilot studies of drug-eluting stents as a marker for restenosis propensity.[7] The mean in-stent late loss observed in a study can be used to predict restenosis risk for bare-metal and drug-eluting stents.[8,9]

We sought to determine whether mean late loss was more stable for stent systems across studies and thus superior to observed clinical restenosis rates for distinguishing drug-eluting stent performance.

Methods

To evaluate the utility of mean late loss to differentiate drug-eluting stent performance, 2 types of data were analyzed. First, a comprehensive literature search was performed to identify the relationship between reported mean late loss and target lesion revascularization (TLR) across studies of different types of stents. Second, primary data from 8 randomized trials of drug-eluting and bare-metal stenting were used to identify predictors of late loss and to standardize the late loss metric for comparison of drug-eluting stents.

Literature Selection and Data Evaluation

A comprehensive literature search of MEDLINE and clinical trials presented at major international meetings (American College of

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Cardiology, Paris Course on Revascularization, Transcatheter Therapeutics, American Heart Association) from January 2003 to April 2005 produced original reports of 46 clinical trials testing drug-eluting or bare-metal stents in the treatment of de novo coronary lesions in which both mean late loss at 4 to 9 months and TLR at 6 to 12 months were reported.[2–7,10–49] For drug-eluting stent trials, at least 2 studies of the same stent were required for inclusion.

Harvard Clinical Research Institute Stent Database

The Harvard Clinical Research Institute (HCRI) Stent Database consists of 8 major clinical trials of stenting of de novo lesions in native coronary arteries conducted during 1996–2003 with the use of either bare-metal stents (STARS, ASCENT, SMART, NIRVANA, EXTRA, CCS) or drug-eluting stents (SIRIUS, E-SIRUS).[4,11,12,22,42,50] Data were derived from the total study sample of 7244 patients and the subgroup with mandated angiographic follow-up (n=3138) performed at 6 months after the index procedure for bare-metal stent studies and at 8 months for drug-eluting stent studies. The end point of interest, in-stent late loss, was complete in 2426 (77%) of those eligible for angiographic follow-up. Informed consent was obtained from each patient, and all investigational sites received approval from their institutional review boards.

Definitions

Acute gain was defined as the MLD immediately after the procedure minus the MLD at baseline. *Late loss* was defined as the MLD immediately after the procedure minus the MLD at angiographic follow-up, within the stent. *Percent diameter stenosis* was defined as [1−(MLD/reference vessel diameter)×100]. *Binary angiographic restenosis* was defined as a >50% diameter stenosis at follow-up. *Lesion length* was defined as the axial extent of the lesion that contained a shoulder-to-shoulder lumen reduction by ≥20%. *Diabetes* was defined as the diagnosis of diabetes mellitus requiring medical treatment.

Statistical Analysis

Binary variables are expressed as frequencies, and continuous variables are expressed as mean±SD. Binary variables were compared with the use of χ^2 analysis, and continuous variables were evaluated by the Student t test. A 2-sided probability value ≤0.05 was considered significant. Linear regression was performed to evaluate the relationship between mean late loss and observed TLR rate across trials. The addition of second-order polynomial terms was performed only when model fit was significantly improved. Statistical analyses were performed in SAS (version 8.2).

Intraclass Correlation: TLR Versus Late Loss

We measured the reliability of TLR versus late loss across 46 trials of bare-metal stent systems and 3 drug-eluting stent systems as estimated by the intraclass correlation coefficients (ρ).[51] We first treated the drug-eluting stent systems and the bare-metal stent systems as 2 classes and estimated the intraclass correlation coefficient. We then estimated intraclass correlation coefficient treating the individual drug-eluting stent systems and bare-metal stents as 4 separate classes. The intraclass correlation coefficient should be highest for the restenosis end point that best discriminates the stent classes. The Mixed Procedure in the SAS statistical package was used to calculate maximum likelihood estimates of the within-class and between-class variance components. The ratio of the between-class variance divided by the sum of the variances was used to estimate the intraclass correlation coefficient for each restenosis end point (ρ_{LL}, ρ_{TLR}). The 2 correlation coefficients were then compared, and a 95% CI for the difference ($\rho_{LL}-\rho_{TLR}$) was constructed by random generation of 1000 bootstrap samples. Finally, to test the robustness of these results without relying on the assumption that all bare-metal stents have the same restenosis properties, the intraclass correlation coefficients were calculated excluding bare-metal stents.

Predictors of Late Loss

A multivariable linear regression model was constructed to predict in-stent late loss with the use of the HCRI Stent Database. Known predictors of restenosis (diabetes mellitus, reference vessel diameter, lesion length, postprocedure residual stenosis, acute gain, and sirolimus-eluting versus bare-metal stent treatment) were evaluated for their relative effects on late loss.

Standardization of Mean Late Loss

Standardization of mean late loss was performed in reference to a representative population derived from the first Food and Drug Administration–approved drug-eluting system,[4,42] with an approximate diabetes prevalence of 25%, median lesion length of 14 mm, and median acute gain of 1.7 mm. The following 2 standardization methods were developed to compare the effectiveness of stents as measured by in-stent late loss in trials that deviate from these expected values.

Standardized Late Loss: Direct Method

If the distribution of all 3 variables (diabetes, lesion length, and acute gain) differs in the new trial compared with the reference population, then the study cohort is divided into 8 subgroups according to the presence or absence of diabetes, lesion length ≥14 or <14 mm, and acute gain ≥1.7 or <1.7 mm. Within each subgroup, we calculate the average late loss and combine these as a weighted average, in which the weights reflect prevalences in the reference population (Appendix A in the online-only Data Supplement: http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.570093/DC1). If patients in a new trial differ from the reference population with respect to diabetes prevalence and median lesion length but have similar acute gain, then only 4 subgroups need to be created.

Although this method of direct standardization has the advantage of simplicity, it requires that the number of patients in the new trial be sufficiently large that stable estimates of mean late loss can be calculated in each of the 8 (or 4) patient subgroups. If this requirement is not met, then the indirect method outlined below should be considered instead.

Standardized Late Loss: Indirect Method

From the reported mean late loss in a new trial and proportions of patients with diabetes mellitus, with lesion length ≥14 mm, and with acute gain ≥1.7 mm, the indirectly standardized late loss can be calculated by comparison with our standardized assumptions: 25% with diabetes; 50% with lesion length ≥14 mm; 50% with acute gain ≥1.7 mm; and multiplication by regression-derived effect estimates (Appendix B in the online-only Data Supplement).

Results

Summary of Stent Trials Reporting Late Loss and TLR

The 46 trials of coronary stenting were tabulated according to stent type in the study if a registry and in each arm if a randomized trial (12 Cypher, 6 TAXUS, 2 ENDEAVOR, 55 bare-metal stent arms; Appendix C in the online-only Data Supplement). Figure 1A depicts the crude positive relationship between late loss means and TLR rates ($P<0.001$, $r^2=0.22$) and the wide variability of TLR rates compared with the more clustered late loss means within stent systems.

Intraclass Correlation of TLR Versus Late Loss

The intraclass correlation coefficient comparing the 2 broad classes (effective drug-eluting stents versus bare-metal stents) was $\rho=0.71$ for mean late loss and $\rho=0.22$ for TLR (95% CI of difference=0.33, 0.65) (Figure 1B). The intraclass correlation coefficient for late loss was again higher when drug-eluting stent types and bare-metal stents were treated as 4 separate classes ($\rho_{LL}=0.68$; $\rho_{TLR}=0.19$; 95% CI of difference=0.24, 0.60). When drug-eluting stent types alone were treated as 3 classes, there was greater separation of the

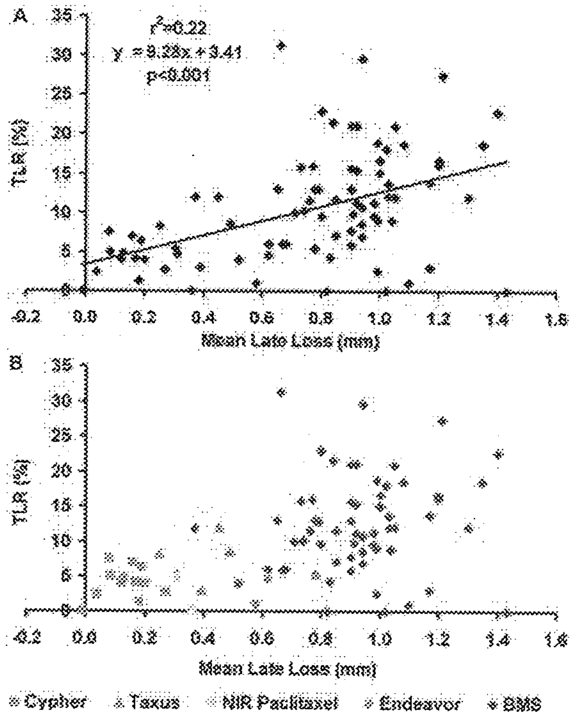

Figure 1. Reliability of mean late loss to discriminate anti-restenotic effect of drug-eluting stents. Mean late loss and TLR rates from each study arm of the 46 trials in Table 1 are shown. A, There is a significant relationship between late loss and TLR (P<0.001). However, the low r^2 reflects the high variability of TLR for any given mean late loss value. A second-order polynomial term did not significantly improve model fit. B, Mean late loss and TLR rates according to stent type. The intraclass correlation coefficient is greater for late loss than for TLR (ρ_{LL}=0.68; ρ_{TLR}=0.19; 95% CI of difference=0.24, 0.60), suggesting greater reliability of the late loss measurement in discriminating anti-restenosis effect. Note that the 2 most rightward-shifted study arms in the Cypher and TAXUS groups are from a study requiring lesions >24 mm in length for inclusion.[37] BMS indicates bare-metal stent.

respective intraclass correlation coefficients (ρ_{LL}=0.64; ρ_{TLR}=0.009; 95% CI of difference=−0.20, 0.92), albeit with decreased power for the comparison because of the reduced sample size.

HCRI Stent Database

Pooled observations from 8 clinical trials yielded 2426 patients with angiographic assessment of late loss at 6 to 8 months (Table 1). The binary angiographic restenosis rates were 28.2% (542/1922) and 7.8% (39/502) in the bare-metal and sirolimus-eluting cohorts, respectively (P<0.0001), and in-stent late losses were 0.94±0.63 and 0.18±0.43, respectively (P<0.0001).

Effect of Reference Vessel Diameter: TLR Versus Late Loss

Reference vessel diameter has previously been shown to be an independent determinant of TLR in both bare-metal and drug-eluting stents.[52] Reference vessel diameter, however, was not a significant determinant of late loss (P=0.12). Late loss was determined by the type of stent used (sirolimus-eluting versus bare-metal), diabetes mellitus, lesion length, and acute gain (Table 2). Residual stenosis was a significant predictor of late loss, but with a small magnitude of effect (0.0097-mm decrease in in-stent late loss per 1% increase in residual stenosis).

Standardized Late Loss and Expected Adjustment Between Trials

To evaluate whether the robustness of the late loss metric could be further improved, we developed 2 methods of standardization for the most influential determinants of late loss that could vary across trials: diabetes mellitus, lesion length, and acute gain (Appendices A and B in the online-only Data Supplement).

Within the trials reported, the magnitude of adjustment of late loss ranged from −0.14 mm to 0.10 mm (Figure 2). The 4 study arms (6%) that had adjustments of >0.10 mm were in trials that enrolled only diabetic patients.[23,40] For >90% of the reported studies, the difference between the unadjusted and adjusted (standardized) late loss was within 0.08 mm, which would result in very small differences in predicted angiographic restenosis rates.[8] Thus, in the majority of drug-eluting stent trials, the unadjusted late loss serves as a stable estimator of binary restenosis propensity.

When limited to drug-eluting stents, separated by stent type, the intraclass correlation coefficient increased with standardization from 0.64 to 0.83. Finally, plotting of either mean or standardized late loss from each study arm resulted in an ordered array of stents (Figure 3).

Discussion

Estimation of treatment effects is subject to bias and confounding when observational and randomized results are evaluated across studies. When restenosis risk factors (diabetes, lesion length, reference vessel size) vary substantially, one can observe markedly different restenosis rates for the

TABLE 1. Baseline and Procedural Characteristics

Characteristic	Overall (n=2426)	Bare-Metal Stents (n=1922)	Sirolimus-Eluting Stents (n=502)	P
Diabetes mellitus	22.4%	22.5%	22.3%	0.95
Reference vessel diameter, mm	2.88±0.50	2.92±0.51	2.73±0.44	<0.0001
Residual percent diameter stenosis, %	7.1±10.0	7.4±10.4	6.2±8.2	0.01
Lesion length, mm	13.4±6.3	13.1±6.4	14.7±5.7	<0.0001
Acute gain, mm	1.71±0.47	1.72±0.48	1.66±0.43	0.005

TABLE 2. Multivariable Predictors of In-Stent Late Loss

Characteristic	Effect Estimate, mm	SE	*P*
Stent type (sirolimus-eluting vs bare-metal)	−0.79	0.029	<0.0001
Diabetes mellitus	0.16	0.028	<0.0001
Lesion length (per 10 mm)	0.17	0.019	<0.0001
Acute gain (per mm)	0.17	0.029	<0.0001
Residual percent diameter stenosis (per 1%)	−0.0097	0.0014	<0.0001
Reference vessel diameter (per mm)	−0.044	0.028	0.12

same stent in different trials or similar restenosis rates between different stent classes (eg, drug-eluting stents versus bare-metal stents). Traditional measures of restenosis, such as binary angiographic and clinical restenosis, are reliable when randomized arms within trials are compared because randomization balances restenosis risk factors, but these measures are not reliable when cohorts across trials are compared.

In-stent late loss is both theoretically and clinically correlated with monotonic and incremental binary restenosis risk.[8,9] In this study we tested the robustness of late loss by considering its reproducibility within different stent systems under a variety of clinical trial conditions. Our findings demonstrate the robustness of late loss in terms of high intraclass correlation under the various reported clinical trials. We evaluated the notion of "stent class" (1) between bare-metal stents and effective drug-eluting stents and (2) between bare-metal stents and different drug-eluting stent systems. We hypothesized that mean late loss might be less subject to variation across studies of the same stent class and therefore might be a more reliable discriminator of drug-eluting stent performance.

In 46 trials of stenting, we found that when the class of bare-metal stents was discriminated from the class of effective drug-eluting stents, late loss was more consistent than TLR rates. The intraclass correlation coefficients for late loss were significantly and substantially higher than for TLR. The

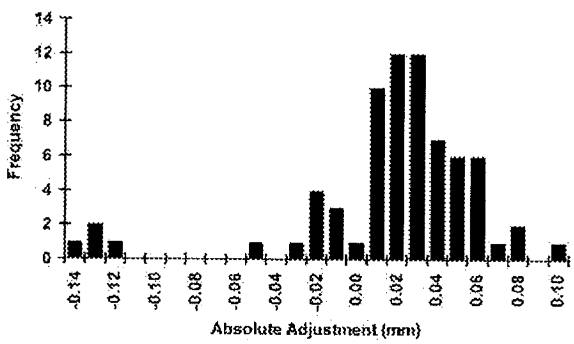

Figure 2. Adjustment in late loss across drug-eluting and bare-metal stent trials. The magnitude of adjustment of late loss for 71 study arms reporting mean late loss, diabetes prevalence, and mean lesion length (indirect method) is shown as a histogram. Greater than 95% of studies had <0.08 mm absolute change between the mean late loss and standardized late loss. The 4 study arms that had adjustments of >0.10 mm were trials that exclusively enrolled diabetic patients.[23,40]

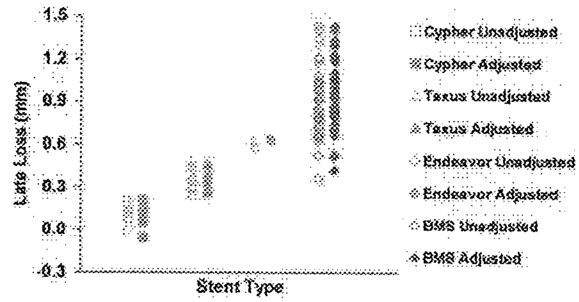

Figure 3. Mean late loss according to stent type. The mean late loss for 71 study arms reporting mean late loss was standardized according to diabetes prevalence and mean lesion length (indirect method), and the values of late loss and standardized late loss were plotted according to categories of stent type. An ordered relationship of stent type exists according to the mean late loss. BMS indicates bare-metal stent.

stability of late loss is due in large part to its direct measurement of narrowing and lack of influence of other factors in its calculation, in contrast to the dependency of TLR rate estimation on reference vessel diameter. Furthermore, late loss was also better at discriminating the individual drug-eluting stent types within the drug-eluting stent class.

Although late loss estimates derived from clinical trials were highly stable, they could be further improved as a comparative metric by standardization, especially in studies with extremely high or low prevalence of risk factors. The magnitude of adjustment required for in-stent late loss, however, was relatively small, underscoring its stability, with 90% of adjustments falling within an absolute 0.08-mm difference from the observed mean value. This is in contrast to the highly variable binary restenosis metrics, which range by as much as 4-fold for TLR when compared in differing patient populations.[3,6]

Is There a "Class Effect" for Drug-Eluting Stents?

The success in preventing coronary restenosis by combining a coronary stent platform with a polymer eluting one of a variety of effective agents (such as sirolimus, paclitaxel, or ABT-578) has led to the common label of drug-eluting stents. Currently, 3 drug-eluting stent systems (Cypher, TAXUS, and ENDEAVOR) have shown substantial reductions in clinical restenosis compared with simpler bare-metal stents in large multicenter randomized trials. Our analysis shows that measures of clinical restenosis, specifically TLR, do not discriminate well between the group of effective drug-eluting stent systems and the group of bare-metal stents. On the other hand, mean late loss in lumen diameter discriminates this group of drug-eluting stents from bare-metal stents with a high degree of separation. Specifically, when trials of effective drug-eluting stents are combined, a clustering at the lower half of the 0.1- to 1.2-mm spectrum of mean late loss is evident (Figure 1), supporting the concept of a class of effective drug-eluting stents.

Not all drug-eluting stent systems have shown effectiveness, however, as different stent, polymer, drug, and dose combinations have yielded markedly different results, some with average late loss exceeding that of bare-metal stents.[18,44]

These examples demonstrate that not all drug-eluting stent systems are equal. In-stent late loss discriminates the differences in restenosis propensity between effective and ineffective drug-eluting stent systems, and thus the notion of a class effect can only be supported for effective stent systems with low in-stent late loss.

Can Late Loss Define Subclasses Within the Class of Effective Drug-Eluting Stents?

Further discrimination by subclass within the class of effective drug-eluting stents was possible in our analysis with the use of late loss. We measured a high intraclass correlation when the 3 effective drug-eluting stent systems were each treated as (sub)classes. Combined with the monotonic relationship between late loss and restenosis,[8] this finding is in contradistinction to the notion advanced by others that there is a late loss "threshold" (such as 0.75 mm for in-stent late loss)[53] below which all drug-eluting stents are exchangeable. As we have shown, when the risk of TLR is low, it is often difficult to distinguish between drug-eluting stents and bare-metal stents in nonrandomized comparisons of TLR rates. In contrast, mean late loss is a reliable indicator of anti-restenosis efficacy across studies, under all levels of TLR risk. In-stent late loss is a reliable and powerful indicator of the restenosis propensity of the stent system under question across the spectrum of bare-metal and drug-eluting stent trial experience, thus supporting the ability to distinguish stent performance within the drug-eluting stent class.

Clinical Application

The primary measure of effectiveness against restenosis for drug-eluting stents is the clinical restenosis rate determined within a randomized trial. These rates vary according to the risk of the population in which the stent is tested, as well as the type of stent used. Stent versus stent randomized trials are designed to control for these population risk factors and allow inference within the trial solely on the efficacy of the assigned stent platform. When deciding which treatment to use for a given patient with obstructive coronary disease, however, physicians may compare the results of several stent systems across different trials. To isolate the efficacy of existing stent systems, one would desire a metric that was consistent from study to study. We have previously shown that late loss is a valid estimator of restenosis risk associated with stents in trials[9] that is also more efficient than clinical or angiographic binary end points.[8] The present analyses demonstrate that when comparisons are made across separate prospective studies, either randomized or observational, late loss is more reliable than restenosis rates at discriminating the effectiveness of different drug-eluting stents. For the practicing physician, in-stent late loss provides a more reliable measure of anti-restenosis propensity than restenosis rates from any given trial source.

The relative invariance of late loss across study populations stands in contrast to the predictable increase in TLR rates or mean percent diameter stenosis with decreasing reference vessel diameter. The translation of incremental differences in late loss to significant increases in clinical restenosis is apparent in studies comparing different drug-eluting stents in higher-risk patient populations[23,48] or in cases in which comparisons are made with greater power.[54]

In the context of diminishing binary rates of restenosis, reliability and power make in-stent late loss a more robust end point than TLR, particularly in early studies to evaluate efficacy, dose-finding studies, or evaluations of the effects of minor variations in stent design. Formal validation of this end point by relating differences in late loss across stent platforms to differences in clinical restenosis will be required for the assumption of true surrogacy. Pragmatically, the ability of late loss to discriminate small differences in efficacy may be informative for pilot or dose-finding studies before the formation of larger studies to evaluate safety and clinical efficacy.

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Handbook of Drug-Eluting Stents

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